REMARKS

I. INTRODUCTION

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

Claims 108 and 110 are requested to be cancelled.

Claims 48, 101, 104, 106, 107, 109 and 111 are currently being amended.

Claims 112-113 are being added.

This amendment adds, changes and/or deletes claims in this application. A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim(s) remain under examination in the application, is presented, with an appropriate defined status identifier.

The amendments to the claims serve to clarify the organ where the treatment of ischemia reperfusion injury is occurring. Support for the claim amendments is found generally throughout the specification, e.g., on page 22, line 9, original claim 42 and previously presented and herein canceled claim 108.

After amending the claims as set forth above, claims 48, 101, 104, 106, 107, 109 and 111-113 are now pending in this application.

II. THE OFFICE ACTION

The Examiner maintains the rejection of claims 48, 101, 104, and 106-111 under 35 U.S.C § 103(a) as obvious over Sonnino et. al. in view of Khau et al. The Examiner concludes that Sonnino teaches or suggests the use of sPLA2 inhibitors for intestinal ischemic-reperfusion injury. Khau et al. teaches 4-substituted-1H-indole-3-glyoxamides as $sPLA_2$ inhibitors. However, there is no suggestion in Sonnino or Khau et al. to combine the teachings to arrive at the presently claimed invention.

or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art references (or references when combined) must teach or suggest all the claim limitations. See MPEP 2142.

Sonnino suggests that intestine contain high amounts of type II sPLA2 which is released during preservation ischemia. Sonnino is limited to intestine and does not suggest that other organs (for example, heart, liver, pancreas, or kidney) would release type II sPLA2 during ischemia *in vivo*. Therefore, one having ordinary skill in the art would not expect similar therapeutic effects in the treatment of ischemia-reperfusion injury occurring in heart, liver, pancreas, or kidney because Sonnino is limited to intestine and for the reasons which follow.

It is well known that a variety factors are involved in ischemia-reperfusion injury (see Lien et al., Life science 74, 543-52, 2003; Attachment A). Lien et al. suggest that the different factor are involved in ischemia reperfusion injury in different organs in different ratios. Therefore, one having ordinary skill in the art would not expect effective treatment of ischemia-reperfusion injury occurring in organs, such as heart, liver, kidney and pancreas (i.e., those other than intestine) based on the teaching of Sonnino which is directed to treating ischemia reperfusion injury in intestine, which contains high levels of type II sPLA2.

It has been established that a Paneth cell of intestine in rat contains high amounts of type II sPLA2. It has been reported in a recent paper that Paneth cells of intestine in rat are stained by Immunohistochemistry, Northern hybridization, or in situ hybridization. On the other hand, liver is weakly stained in only Immunohistochemistry (Nyman et al., J Histochem Cytochem 48, 1469-77, 2000; Attachment B). Another paper (Yoshikawa e tal., J Histochem Cytochem 49, 777-82, 2001; Attachment C) also reports that mRNA of type II PLA2 is not detected in liver. These reports show that distribution of type II PLA2 varies according to organ. Therefore, the effective treatment of organs containing a small amount of type II sPLA2 cannot be rendered obvious by the result of treatment of ischemia reperfusion injury in intestine which contains high amounts of type II PLA2.

In sum, Sonnino and Khau do not render the present invention obvious because one having ordinary skill in the art would not expect that treatment of ischemia-reperfusion injury occurring in e.g., heart, liver, pancreas and kidney, would proceed similarly to treatment of ischemia reperfusion injury in intestine based on the low or undetectable levels of type II sPLA2 in e.g., heart, liver, pancreas or kidney. Furthermore, one having ordinary skill in the art would not have motivated to extend the use of an sPLA2 inhibitor, such as, [(3-(2-amino-1,2-dioxoethyl)-2-ethyl-1-(phenylmethyl)-IH-indole-4-yl]oxy]acetic acid, for the treatment of ischemia-reperfusion injury occurring in heart, liver, pancreas, or kidney, where the prior art teaches only a organ having high levels of type II sPLA2, i.e., intestine has been shown to be effectively treated.

Sonnino fails to teach or suggest treating ischemia reperfusion injury in heart, liver, pancreas or kidney. The references cited herein clearly teach the differences between levels of type II sPLA2 in intestine versus heart, liver, pancreas and kidney. Furthermore, the references herein teach that other factors contribute to ischemia reperfusion injury in heart, liver, pancreas and kidney. In fact, Nyman and Yoshikawa clearly teach that sPLA2 is weakly detected, if detected at all, in liver cells. This disclosure and the disclosure of Lien clearly teach away from the suggestion that an sPLA2 inhibitor, useful in treating ischemia reperfusion injury in intestine, would also be useful in treating ischemia reperfusion injury in heart, liver, pancreas and kidney.

Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

III. CONCLUSION

Applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment,

to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

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